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(54) Diabetes management

(57) A method of predicting the level of the HbA_{1C} component of glycosylated haemoglobin in a patient's blood. A mathematical model is derived which predicts the behaviour of the HbA_{1C} component level relative to the blood glucose level using previously measured HbA_{1C} and blood glucose levels. The model is updated each time a new HbA_{1C} level is measured using that new measurement and recent new blood glucose level measurements. The updated model is then applied to predict the HbA_{1C} level, between measurements of that level, using measurements of blood glucose level obtained since the last HbA_{1C} measurement.

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Description

The present invention relates to the management of diabetes and more particularly to a method and apparatus for monitoring the effectiveness of diabetes treatment.

In the treatment of diabetes, a patient is required to regularly check his blood glucose level using a self-testing kit. By comparing the result of a self-test with the blood glucose level which he would consider normal, the patient is able to estimate the amount of insulin which should be taken in order to bring his blood glucose level back towards that normal. Self-testing kits used for this purpose have today become very sophisticated and reliable and provide an excellent means for the short term control of diabetes. However, diabetic patients can also suffer problems arising from their condition which only become apparent in the longer term. An individual blood glucose measurement obtained by a self-test provides little or no indication of the onset of such long term problems.

The basic problem which diabetic patients have relates to the transfer of sugar, contained in the blood, across cell membranes. This problem in turn makes it difficult for the body to maintain sugar levels in the blood at the correct level. Too much blood sugar (e.g. due to the patient injecting too little insulin) and the patient becomes hyperglycaemic whilst too little blood sugar (e.g. due to the patient injecting too much insulin) may cause the patient to become hypoglycaemic. In particular, excessive levels of sugar in the blood result in sugar combining with protein to form glycosylated protein. Glycosylated protein is substantially insoluble and gives rise to thickening of the walls of veins and arteries, and thickening of the myelination of nerves.

One particular form of glycosylated protein is glycosylated haemoglobin. As glycosylated haemoglobin tends to remain in the blood in the long term, it provides an excellent indication of the level of glycosylated protein in the blood and therefore of the effectiveness of the treatment regime which a patient has been following, as well of course as indicating how well the patient is following that regime.

Glycosylated haemoglobin is composed of three components; namely HbA_{1A}, HbA_{1B}, and HbA_{1C}. The HbA_{1C} level in particular is commonly measured by laboratory test in order to provide information on the long term effectiveness of diabetes treatment. The HbA_{1C} level reflects the effectiveness of blood glucose treatment over the 6-8 week period preceding the HbA_{1C} measurement. It has been shown that a low level of HbA_{1C} in a diabetic patient's blood is a good indication that the treatment regime is effective and that the risk of secondary problems related to glycosylated haemoglobin is low. The level of HbA_{1C} in a healthy person's blood is between 4 and 6 % of the total haemoglobin whilst in a diabetic person the level may be significantly higher (e.g. greater than 8%). It is generally sought to reduce the level of HbA_{1C} in a diabetic patient's blood to between 6 and 7%.

Due to the often scarce nature of health service resources, and for the sake of convenience and practicality, the HbA_{1C} level in a patient's blood is generally tested only every 3 to 4 months. However, given that the HbA_{1C} level provides an indication of the effectiveness of treatment over the previous 6 to 8 weeks, long periods of ineffective treatment, and therefore damage to a patient's health, can go undetected with current testing regimes.

The article 'A Theoretical Model to Predict the Behaviour of Glycosylated Hemoglobin Levels' by Kirk W. Beach, J. theor. Biol. (1979) 81,547-561, describes a mathematical model for predicting the level of glycosylated haemoglobin from the blood glucose level. This model is however extremely crude and makes use of the simplification that the blood glucose level is either constant, changing only by way of a small number of discrete steps, or varying sinusoidally. Application of the model to a real patient necessarily involves a great over-simplification of the behaviour of blood glucose levels.

It is an object of the present invention to overcome or at least mitigate disadvantages of known diabetes management techniques.

It is a further object of the present invention to provide a method and apparatus for providing a substantially continuous estimate of glycosylated haemoglobin component levels.

According to a first aspect of the present invention there is provided a method of predicting the level of a glycosylated haemoglobin component in a patient's blood using previously measured blood glucose and glycosylated haemoglobin component levels, the method comprising:

deriving a mathematical model of the behaviour of the glycosylated haemoglobin component level relative to the blood glucose level using previously measured levels;

updating the model when a new glycosylated haemoglobin component level is measured using that new measurement and recent new blood glucose level measurements; and

applying the mathematical model to predict the glycosylated haemoglobin component level, between measurements of that level, using measurements of blood glucose level obtained since the last glycosylated haemoglobin component measurement.

Typically, blood glucose level measurements are made at a considerably higher frequency than glycosylated haemoglobin component measurements. The method of the present invention may therefore be used to predict the current

glycosylated haemoglobin component level in a patient's blood using blood glucose level measurements obtained since the last glycosylated haemoglobin component level measurement. As the model is updated each time a new HbA_{1C} measurement is made, the model is capable of tracking changes in the physiology of the patient which cause the behaviour of the HbA_{1C} level to change with respect to the blood glucose level. Changes in the blood glucose measurement pattern, i.e. the times at which the patient makes blood glucose measurements, can also be accounted for.

Preferably, the mathematical model is a parametric model or a semi-parametric model, where the model is defined by one or more model coefficients and a model equation which relate blood glucose level to the glycosylated haemoglobin component level. More preferably, the model equation relates the glycosylated haemoglobin component level to one or more parameters which describe, at least in part, the behaviour (e.g. distribution) of the blood glucose level over a preceding, relatively short, time interval.

The model equation may be a linear equation in which case said model coefficients are the linear coefficients of the equation. The linear equation is of the form:

$$y = p_1 h_1 + p_2 h_2 + \ldots + p_q h_q + c$$

where y is the predicted glycosylated haemoglobin level, p are the linear model coefficients, h are the parameters which describe blood glucose level behaviour, and c is a constant.

Preferably, the behaviour of the blood glucose level over said short time intervals may be described using one or more gaussian functions which model the distribution of blood glucose level measurements. Said one or more parameters (h) may be chosen from the mean, variance, and amplitude of the gaussian function(s) or may be derived therefrom.

In the case of a parametric or semi-parametric model, the model may be updated following each glycosylated haemoglobin component level measurement by recalculating said model coefficients (p). In an alternative embodiment of the present invention, the coefficients of the parametric model are adapted following each new glycosylated haemoglobin level measurement using an adaptive algorithm. One suitable adaptive algorithm is Widrows algorithm. Such adaptive algorithms are arranged to reduce the error between the predicted glycosylated haemoglobin level and the measured glycosylated haemoglobin level.

The glycosylated haemoglobin component predicted using the method of the above first aspect of the present invention is one of HbA_{1A}, HbA_{1B}, and HbA_{1C}. Preferably however, the predicted component is HbA_{1C}.

The method of the above first aspect of the present invention may comprise:

transmitting measured glucose levels via a wireless data transmission link from a remote station, available to the patient, to a central data processing station;
carrying out said steps of deriving the mathematical model, updating the model, and predicting the glycosylated haemoglobin component at the central processing station using the transmitted measurements and previous measurement data stored at the central station; and
transmitting predicted glycosylated haemoglobin component levels back to the remote station via the wireless data transmission link.

Preferably, the remote station is a mobile telephone or a two-way pager whereby the wireless data transmission link is provided by a mobile telephone network. For example, the telephone network may be a GMS network and the data may be transmitted by the short message service (SMS). It is to be understood that the term 'mobile telephone' as used here refers to any portable device which utilises wireless telephonic communication including conventional cellular telephones and combined cellular telephone/personal data assistant (PDA) devices.

Alternatively, the method may comprise carrying out all of the steps of the method of the above first aspect of the invention in a portable monitoring device.

It will be appreciated that the method of the present invention may be applied to blood taken from a human or animal patient.

According to a second aspect of the present invention there is provided a method of predicting the level of a glycosylated haemoglobin component in a patient's blood, the method comprising the steps of:

transmitting a blood glucose measurement from a remote station to a central processing station;
predicting at the central station a glycosylated haemoglobin component level for the patient's blood using said transmitted measurement and a mathematical model of the glycosylated haemoglobin component level relative to blood glucose level; and
transmitting the predicted glycosylated haemoglobin component level from the central station to the remote station.

According to a third aspect of the present invention there is provided a system for predicting the level of a glycosylated haemoglobin component in a patient's blood using previously measured blood glucose and glycosylated haemoglobin component levels, the system comprising:

means for deriving a mathematical model of the behaviour of the glycosylated haemoglobin component level relative to the blood glucose level using previously measured levels, and for updating the model when a new glycosylated haemoglobin component level is measured using that new measurement and recent new blood glucose level measurements; and
memory means for storing said model and/or the updated model and measured blood glucose and glycosylated haemoglobin component levels;
means for applying the mathematical model to predict the glycosylated haemoglobin component level, between measurements of that level, using measurements of blood glucose level obtained since the last glycosylated haemoglobin component measurement.

In a preferred embodiment of the system of the above third aspect of the present invention, said means for deriving and applying and said memory means are provided by a central computer, the system further comprising a mobile telephone or two-way pager for conveying measurement data to the central computer via a wireless data transmission link. The system may be further arranged to convey predicted glycosylated haemoglobin component levels from the central station to the mobile telephone or two-way pager.

For a better understanding of the present invention and in order to show how the same may be carried into effect reference will now be made, by way of example, to the accompanying drawings, in which:

Figure 1 shows HbA_{1C} level measurements together with blood glucose level measurements obtained from a diabetic patient over a period of 640 days;

Figures 2A to 2D show respective sets of blood glucose level measurements, extracted from the measurements shown in Figure 1, for periods preceding four HbA_{1C} level measurements;

Figures 3A to 3D show respectively predicted blood glucose level distributions for each of the measurement windows of Figures 2A to 2D;

Figure 4 is a flow chart illustrating a method used to predict HbA_{1C} levels;

Figure 5 shows measured HbA_{1C} levels of Figure 1 together with predicted HbA_{1C} levels; and

Figure 6 illustrates schematically apparatus for implementing the method of Figure 5.

The method described below for predicting HbA_{1C} levels in the blood of a patient is illustrated using actual blood glucose and HbA_{1C} measurements obtained from a human patient. Figure 1 shows the measured blood glucose and HbA_{1C} levels plotted against time (measured in days) over a period of 640 days. As discussed above, HbA_{1C} measurements are typically made at relatively infrequent intervals (every 12 to 16 weeks) whilst blood glucose level measurements are made much more frequently (typically two to five times a day).

Let Y be the set of N available HbA_{1C} measurements y_n shown in Figure 1, where $Y = \{y_1 \ldots y_N\}$ and each measurement corresponds to a measurement time $t = T_n$, (n = 1 to N). Similarly, let X be the set of M available blood glucose measurements x_m also shown in Figure 1, where $X = \{x_1 \ldots x_M\}$ and each measurement corresponds to a measurement time $t = t_m$, (m = 1 to M). The set of blood glucose measurements X is divided into sub-sets X_n, each sub-set being associated with the corresponding HbA_{1C} measurement Y_n and containing those values obtained in the period $t > T_n$ -65 days to T_N. It is noted that when the interval between consecutive HbA_{1C} is less than 65 days, adjacent sub-sets X_n will overlap. For the data of Figure 1, with twelve HbA_{1C} measurements, twelve sub-sets of blood glucose measurements are obtained, the first four of these being shown in Figures 2A to 2D for the purpose of illustration.

A suitable semi-parametric model is applied to each sub-set of blood glucose level measurements X_n to model the distribution of the measurements within the set (i.e. to model the probability density function). The model is chosen to have a relatively small number of parameters. In the present example, the distribution of each sub-set X_n is modeled using the sum of a pair of gaussian functions:

$$P(l) = kG(l|\mu_1, \sigma_1^2) + (1-k)G(l|\mu_2, \sigma_2^2) \tag{1}$$

where k is a coefficient and $0 \le k \le 1$, l is the blood glucose level, and the gaussian function G has the form:

$$G(l) = \frac{1}{2\pi\sigma^2}\exp\left\{-\frac{(l-\mu)^2}{2\sigma^2}\right\} \qquad (2)$$

The means (μ_1,μ_2) and variances (σ_1^2,σ_2^2) of the gaussian functions, as well as the coefficient k, are obtained using the expectation-maximization algorithm (see Dempster A.P., Laird N.M., and Rubin, D.B. (1977); 'Maximum Likelihood from Incomplete Data via the EM Algorithm'; J. Royal Statistical Soc.; B 39 (1); 1-38). The modeled distribution for each of the sub-sets of blood glucose measurements are shown in Figures 3A to 3D.

Each model can be represented by a parameter vector Θ_n $\{\mu_{n1}, \mu_{n2}, \sigma_{n1}^2, \sigma_{n2}^2, k\}$. A suitable combination of parameters is selected from the parameter vector Θ_n and is used to form a model vector h_n at time T_n. In the present example the parameters μ_1, μ_2, σ_1^2 and a constant 1 are selected, corresponding respectively to h_{n1}, h_{n2}, h_{n3} and h_{n4} of the model vector. The model vectors h_n and the measured HbA_{1C} levels y_n are used to form the rows of a model specification matrix H and an observation vector z respectively and the linear problem $z = Hp$ constructed, where p is a regression coefficient vector. This problem can be more fully written as the matrix equation:

$$\begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_N \end{bmatrix} = \begin{bmatrix} h_{11} & h_{12} & h_{13} & h_{14} \\ h_{21} & h_{22} & h_{23} & h_{24} \\ \vdots & \vdots & \vdots & \vdots \\ h_{N1} & h_{N2} & h_{N3} & h_{N4} \end{bmatrix} \begin{bmatrix} p_1 \\ p_2 \\ p_3 \\ p_4 \end{bmatrix} \qquad (3)$$

An estimate of the regression coefficient vector p can be determined from:

$$\hat{p} = H^{-1} z \qquad (4)$$

where H^{-1} is the inverse of the matrix H (or pseudo inverse in the case that H is not square or is singular) and can be obtained using a singular value decomposition technique (Press, W.H. Teukolsky, S.A. Vetterling, W.T. Flannery, B.P. 1992, 'Numerical Recipes in C: The Art of Scientific Computing', 2nd ed. Cambridge University Press). The estimated regression coefficient vector $\hat{p}$ can then be used to predict a future HbA_{1C} level y_{N+1} from the model vector h_{N+1}, derived from the sub-set of blood glucose measurements X_{N+1}, i.e.:

$$y_{N+1} = p_1 h_{N+1,1} + p_2 h_{N+1,2} + p_3 h_{N+1,3} + p_4 h_{N+1,4}. \qquad (5)$$

Figure 4 is a flow diagram outlining the main steps of this method of predicting HbA_{1C} levels.

As has been explained above, changes in the physiology of a patient are likely to change the behaviour of the HbA_{1C} level with respect to blood glucose level. It is therefore important that the coefficients of the regression coefficient vector $\hat{p}$ be updated regularly. This can be achieved by recalculating the vector $\hat{p}$ every time a new HbA_{1C} measurement is made. Typically, for a patient with no previous records, the regression coefficient vector is first derived using data obtained from a number of other patients. Each time a new HbA_{1C} measurement is made, the new HbA_{1C} measurement, together with the blood glucose measurements obtained since the last HbA_{1C} measurement, is used in the recalculation of the regression coefficient vector. Assuming that the value of N is maintained constant by removing the earliest obtained measurements in turn, after N HbA_{1C} measurements have been obtained from the subject patient, the estimated regression coefficient vector will be derived solely from measurements made on the subject patient.

In order to improve the accuracy with which the HbA_{1C} level can be predicted, and more particularly to avoid biasing of the result by rogue measurements, an estimated regression coefficient vector $\hat{p}$ is in fact obtained for N different data sets, omitting in turn each of the elements y_1 to y_N of the above matrix equation together with the corresponding row of the matrix H. The mean of the estimated regression coefficient vectors is then obtained after removing the top and bottom 10% of each of the vector components. For the data set shown in Figure 1, the final estimated regression coefficient vector is the trimmed mean of twelve estimated vectors $\hat{p}$. The coefficients of this final regression coefficient vector can then be used to predict the current HbA_{1C} level using equation (5) above. Figure 5 shows HbA_{1C} levels

predicted using a model obtained with this method together with the measured HbA_{1C} levels used to formulate the model (and as shown in Figure 1). It can be seen that the predicted values closely follow the measured values.

Further improvements in prediction accuracy may be achieved by increasing the number of parameters *p*, by increasing the size of the model vector h_n, e.g. to additionally include δ_2. Alternatively, a set of HbA_{1C} estimates may be made using a corresponding set of parametric models, each model being obtained using a different set of parameters, e.g. μ_1, $\mu_2, \sigma_1^2), k$ or μ_1, μ_2, σ_2^2, k. Accuracy may also be increased by appropriately transforming (e.g. log, exponential) one or more of the parameters.

It is well known that blood glucose levels in a patient fluctuate periodically according to the time of day and more particularly according to whether or not the patient has just eaten. It may therefore be more accurate to separately model blood glucose levels for different times of day. This technique requires the separation of all blood glucose levels into separate sets. There might, for example, be nine sets, i.e. measurements made before and after breakfast, lunch, dinner, and evening snack. For each set j, a set of parameter vectors Θ_n^j is obtained, where $n = 1 \cdots N$. Again, for each value of *n*, a set of suitable parameters are selected to form the model vector h_n. The estimated regression coefficient vector $\hat{p}$ can then be obtained as described above.

Given that the calculation of the regression coefficient vector may involve a considerable amount of stored data (e.g. up to two years of measurement data), and hence present a considerable degree of computational complexity, it is desirable to store the measurement data and perform computations at a central data processing unit available to many patients. In addition, this arrangement improves data security and, importantly, allows the algorithm by which HbA_{1C} levels are predicted to be easily and quickly updated, should that prove necessary.

Figure 6 illustrates a diabetic management system where each patient in the system is provided with a portable electronic blood glucose measurement unit 1 of known type. This unit is modified for coupling measured blood glucose levels via an interface 2, for example a notebook computer or PC, to a mobile telephone 3. The measurement data is then transmitted via the mobile telephone network to a central data processing station 4 of the type described above. Based on recently received blood glucose measurements, and a precalculated regression coefficient vector, the central processing station 4 estimates the patient's HbA_{1C} level. The regression coefficient vector can be updated each time a HbA_{1C} measurement is made on the patient either using data entered directly into the central data processing station or transmitted to it from, for example, a doctor's surgery. The predicted HbA_{1C} level can be almost immediately transmitted back to the patient's mobile phone 3, via the telephone network, where it can be displayed on the phone 3 or the interface 2. By integrating the functions of the mobile phone 3, the interface 2, and the measurement unit 1, the patient can be provided with a truly portable HbA_{1C} level monitoring system.

It will be appreciated by the skilled person that other modifications may be made to the above described embodiment without departing from the scope of the present invention. For example, the probability density function of each set of blood glucose levels X_n may be modeled using one or more gamma functions as an alternative to gaussian functions.

Claims

1. A method of predicting the level of a glycosylated haemoglobin component in a patient's blood using previously measured blood glucose and glycosylated haemoglobin component levels, the method comprising:

    deriving a mathematical model of the behaviour of the glycosylated haemoglobin component level relative to the blood glucose level using previously measured levels;
    updating the model when a new glycosylated haemoglobin component level is measured using that new measurement and recent new blood glucose level measurements; and
    applying the mathematical model to predict the glycosylated haemoglobin component level, between measurements of that level, using measurements of blood glucose level obtained since the last glycosylated haemoglobin component measurement.

2. A method according to claim 1, wherein the mathematical model is a parametric model or a semi-parametric model and is defined by one or more model coefficients and a model equation which relate blood glucose level to the glycosylated haemoglobin component level.

3. A method according to claim 2, wherein the model equation relates the glycosylated haemoglobin component level to one or more parameters which describe behaviour of the blood glucose level over a preceding, relatively short, time interval.

4. A method according to claim 3, wherein the model equation is a linear equation having the form:

$$y = p_1h_1 + p_2h_2 + \ldots + p_qh_q + c$$

where y is the predicted glycosylated haemoglobin level, p are the linear model coefficients, h are the parameters which describe blood glucose level behaviour, and c is a constant.

5. A method according to claim 3 or 4, wherein the behaviour of the blood glucose level over said short time intervals is described using one or more parametric functions which model the distribution of blood glucose level measurements and said one or more parameters (h) are selected from or derived from the parameters defining these functions.

6. A method according to claim 5, wherein the or each said function is a gaussian function and said one or more parameters (h) are chosen from or are derived from the mean, variance, and amplitude of the gaussian function(s).

7. A method according to any one of claims 2 to 6, wherein the model is updated following a glycosylated haemoglobin component level measurement by recalculating said model coefficients (p).

8. A method according to any one of claims 2 to 6, wherein the coefficients of the parametric model are adapted following a new glycosylated haemoglobin level measurement using an adaptive algorithm.

9. A method according to any one of the preceding claims, wherein the glycosylated haemoglobin component predicted is HbA_{1C}.

10. A method according to any one of the preceding claims and comprising:

transmitting measured glucose levels via a wireless data transmission link from a remote station, available to the patient, to a central data processing station;
carrying out said steps of deriving the mathematical model, updating the model, and predicting the glycosylated haemoglobin component at the central processing station using the transmitted measurements and previous measurement data stored at the central station; and
transmitting predicted glycosylated haemoglobin component levels back to the remote station via the wireless data transmission link.

11. A method according to claim 10, wherein the remote station is a mobile telephone or a two-way pager whereby the wireless data transmission link is provided by a mobile telephone network.

12. A method of predicting the level of a glycosylated haemoglobin component in a patient's blood, the method comprising the steps of:

transmitting a blood glucose measurement from a remote station to a central processing station;
predicting at the central station a glycosylated haemoglobin component level for the patient's blood using said transmitted measurement and a mathematical model of the glycosylated haemoglobin component level relative to blood glucose level; and
transmitting the predicted glycosylated haemoglobin component level from the central station to the remote station.

13. A system for predicting the level of a glycosylated haemoglobin component in a patient's blood using previously measured blood glucose and glycosylated haemoglobin component levels, the system comprising:

means (4) for deriving a mathematical model of the behaviour of the glycosylated haemoglobin component level relative to the blood glucose level using previously measured levels, and for updating the model when a new glycosylated haemoglobin component level is measured using that new measurement and recent new blood glucose level measurements;
memory means (4) for storing said model and/or the updated model and measured blood glucose and glycosylated haemoglobin component levels; and
means (4) for applying the mathematical model to predict the glycosylated haemoglobin component level, between measurements of that level, using measurements of blood glucose level obtained since the last glycosylated haemoglobin component measurement.

14. A system according to claim 13, wherein said means for deriving and applying and said memory means are provided by a central computer (4), the system further comprising a mobile telephone or two-way pager (3) for conveying measurement data to the central computer (4) via a wireless data transmission link.

15. A system according to claim 14 and comprising a blood glucose measurement unit (1) coupled to the mobile telephone or two-way pager for transmitting blood glucose level measurements to the mobile telephone or two-way pager.

16. A system according to claim 14 or 15 and which is arranged to convey predicted glycosylated haemoglobin component levels from the central station (4) to the mobile telephone or two-way pager (3).

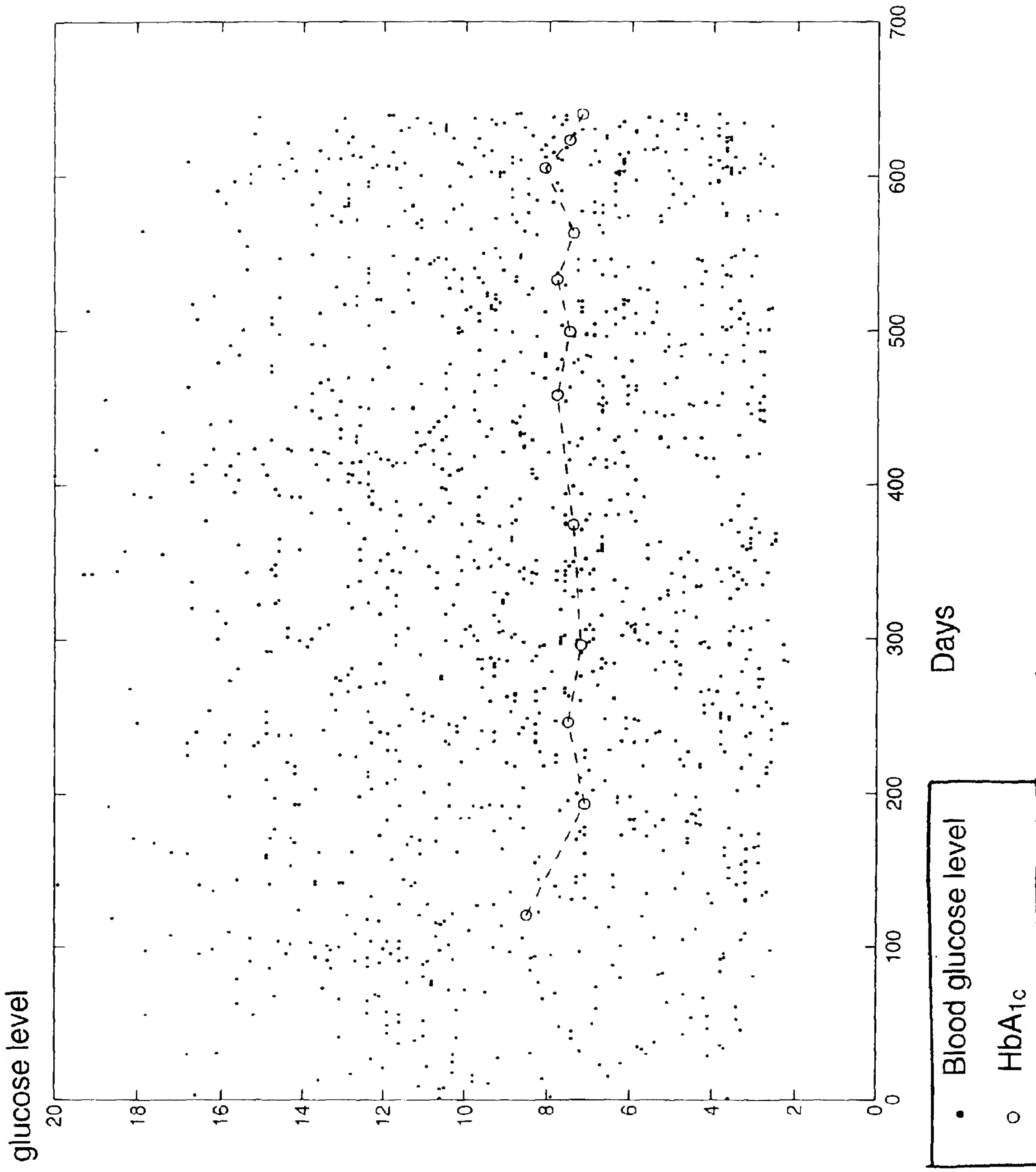
Blood glucose level
0
2
4
6
8
10
12
14
16
18
20
0
100
200
300
400
500
600
700
Days
Blood glucose level
HbA1c

Figure 1

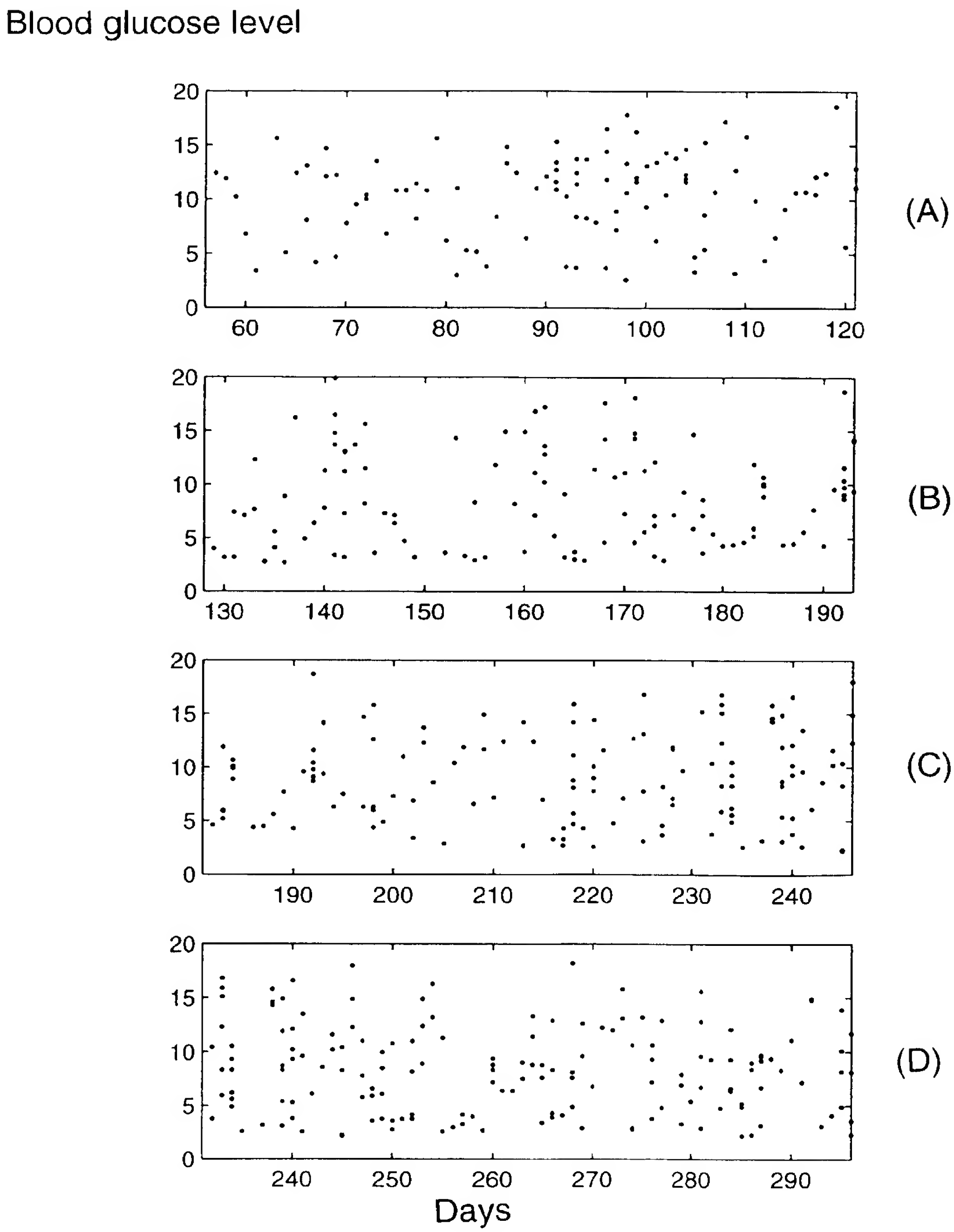
Blood glucose level
20
15
10
5
0
60
70
80
90
100
110
120
(A)
130
140
150
160
170
180
190
(B)
190
200
210
220
230
240
(C)
240
250
260
270
280
290
Days
(D)

Figure 2

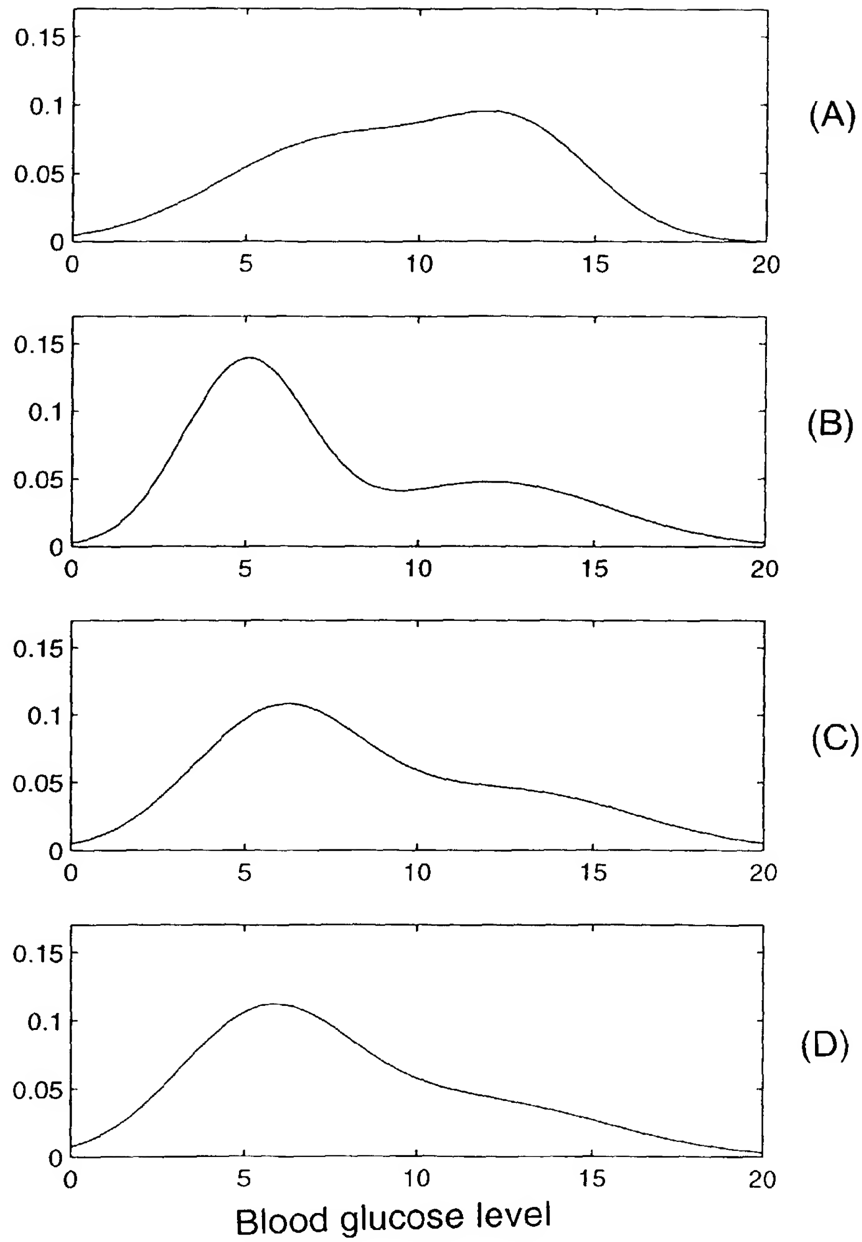

Figure 3

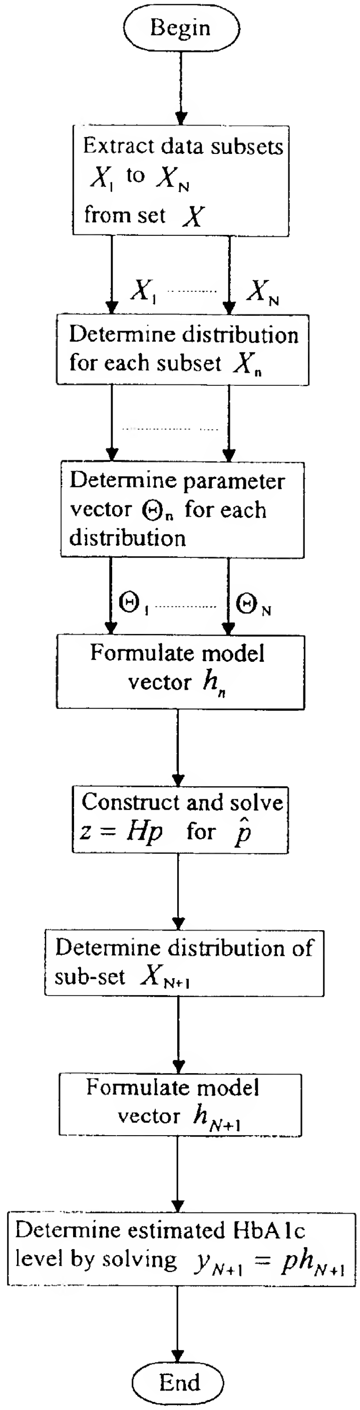
Begin
Extract data subsets X_1 to X_N from set X
X_1 .... X_N
Determine distribution for each subset X_n
Determine parameter vector Θ_n for each distribution
Θ_1 .... Θ_N
Formulate model vector h_n
Construct and solve $z = Hp$ for $\hat{p}$
Determine distribution of sub-set X_{N+1}
Formulate model vector h_{N+1}
Determine estimated HbA1c level by solving $y_{N+1} = ph_{N+1}$
End

Figure 4

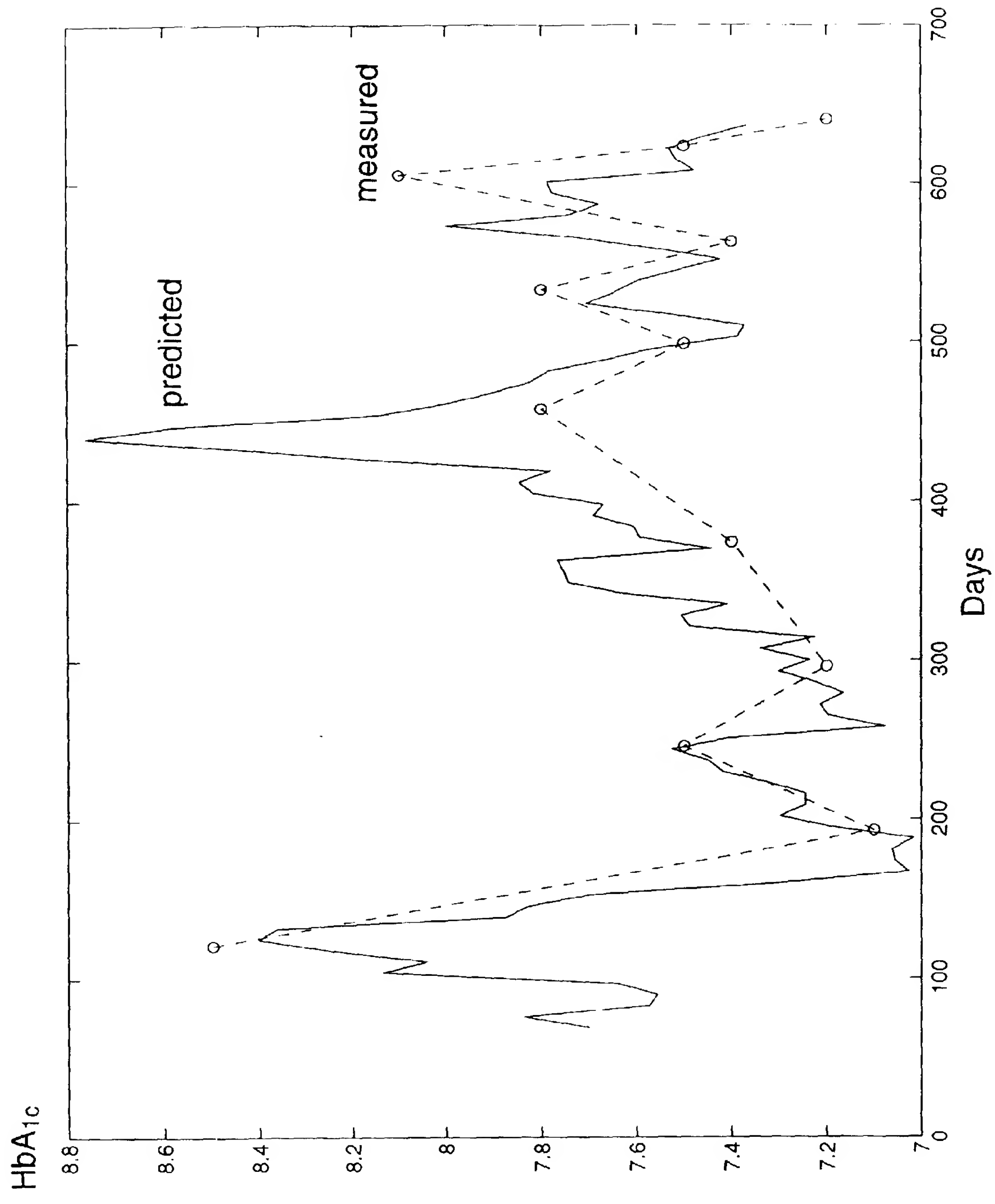
HbA1c
8.8
8.6
8.4
8.2
8
7.8
7.6
7.4
7.2
7
0
100
200
300
400
500
600
700
predicted
measured
Days

Figure 5

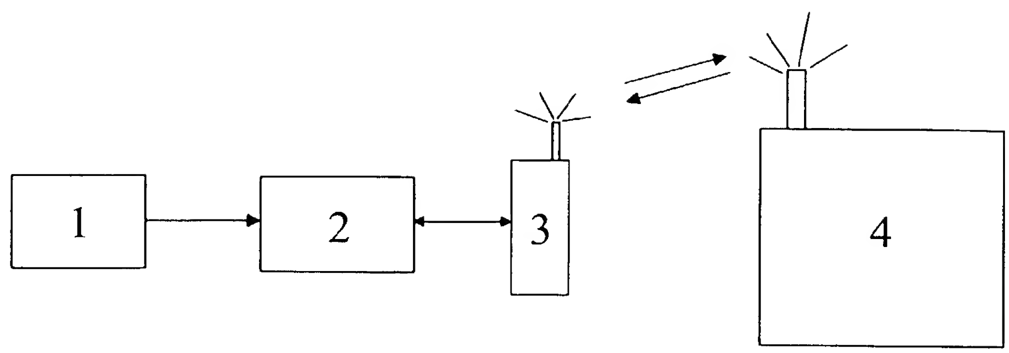

Figure 6

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number
EP 98 66 0040

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	FR 2 710 438 A (BRETAGNE RADIOCOMMUNICATIONS) 31 March 1995 * the whole document * ---	13-16	G01N33/72 G01N33/66 A61B5/00
X	E. J. GOMEZ ET AL.: "A telemedicine distributed decision-support system for Diabetes management" PROCEEDINGS OF THE ANNUAL INTERNATIONAL CONFERENCE OF THE IEEE ENGINEERING IN MEDICINE AND BIOLOGY SOCIETY., vol. 14, November 1992, pages 1238-1239, XP000480765	13	
Y	* the whole document * ---	14-16	
Y	US 5 415 167 A (P. J. WILK.) 16 May 1995 * column 8, line 30 - line 34 * * column 10, line 31 - line 48 * ---	14-16	
A	WO 95 33996 A (SELFCARE, INC.) 14 December 1995 * the whole document * -----	13-16	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

G01N
A61B

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

13-16

Claims searched incompletely :

Claims not searched :

1-12

Reason for the limitation of the search:

ARTICLE 52(2)(a), EPC. :- Mathematical Method

Place of search	Date of completion of the search	Examiner
THE HAGUE	8 September 1998	Griffith, G

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